PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrITOVEBI®

inavolisib tablets

Tablets, 3 mg and 9mg, Oral

Antineoplastic agent

Hoffmann-La Roche Limited
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Mississauga, ON L5N 5M8

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**RECENT MAJOR LABEL CHANGES**

Not Applicable.

**TABLE OF CONTENTS**

**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

ITOVEBI® (inavolisib film-coated tablets), in combination with palbociclib and fulvestrant, is indicated for:

- the treatment of adult patients with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine treatment (see 14 CLINICAL TRIALS).

### 1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (<18 years of age).

### 1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of ITOVEBI did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger patients.

## 2 CONTRAINDICATIONS

- ITOVEBI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

- **Hyperglycemia.** Severe case of hyperglycemia have been reported. The safety of ITOVEBI in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment have not been studied. Metformin prophylaxis is recommended for patients with risk factors for hyperglycemia.

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

Treatment with ITOVEBI should be initiated by a physician experienced in the use of anticancer therapies.

Patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer should be selected for treatment with ITOVEBI based on the presence of one or more *PIK3CA* mutations using a validated test. *PIK3CA* mutation status should be established prior to initiation of ITOVEBI therapy.

The use of ITOVEBI is not recommended in patients with moderate (eGFR≥ 30 to < 60 mL/min based on CKD-EPI) or severe (eGFR < 30 mL/min based on CKD-EPI) renal impairment.

### 4.2 Recommended Dose and Dosage Adjustment

Dose Recommendation:
The recommended dose of ITOVEBI is 9 mg taken orally once daily with or without food.

ITOVEBI should be administered in combination with palbociclib and fulvestrant. The recommended dose of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. The recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 0, 14, and 28, then every 28 days thereafter. Refer to the prescribing information for palbociclib and fulvestrant for complete dosing information.

Treatment of pre/perimenopausal women with ITOVEBI should also include a luteinizing hormone-releasing hormone (LHRH) agonist in accordance with local clinical practice.

For male patients, consider treatment with an LHRH agonist according to local clinical practice.

Duration of Treatment:

It is recommended that patients are treated with ITOVEBI until disease progression or unacceptable toxicity.

Dose Modification:

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with ITOVEBI. ITOVEBI treatment should be permanently discontinued if patients are unable to tolerate the 3 mg daily dose (see Table 1).

The recommended dose reduction guidelines for adverse reactions are listed in Table 1.

**Table 1**: **Dose Reduction Guidelines for Adverse Reactions**

| Dose Reduction Schedule | Dose Modified |
|---|---|
| Starting dose | 9 mg daily |
| First dose reduction | 6 mg daily |
| Second dose reduction | 3 mg daily |

The dose of ITOVEBI may be re-escalated to a maximum daily dose of 9 mg based on clinical evaluation of the patient by the treating physician.

The recommended dosage modifications of ITOVEBI for adverse reactions are summarized in

Table **2**.

**Table 2: Dose Modification and Management for Adverse Reactions**

| Adverse Reaction | Severity | Recommendation |
|---|---|---|
| Hyperglycemia[b] | Fasting glucose level[a] > ULN to 160 mg/dL (> ULN - 8.9 mmol/L) | • No dose adjustment of ITOVEBI required.<br>• Consider dietary modifications (e.g., low carbohydrate diet) and ensure adequate hydration.<br>• Consider initiating or intensifying oral anti-hyperglycemic medications[c] for patients with risk factors for hyperglycemia[d] |
| | Fasting glucose level > 160 to 250 mg/dL (> 8.9 – 13.9 mmol/L) | • Interrupt ITOVEBI until fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L).<br>• Initiate or intensify anti-hyperglycemic medication[c,e].<br>• Resume ITOVEBI at the same dose level.<br>• If fasting glucose level persists > 200 – 250 mg/dL (> 11.1 – 13.9 mmol/L) for 7 days under appropriate anti-hyperglycemic treatment, consultation with a healthcare professional experienced in the treatment of hyperglycemia is recommended. |
| | Fasting glucose level > 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L) | • Interrupt ITOVEBI.<br>• Initiate or intensify anti-hyperglycemic medication[c,e].<br>• Administer appropriate hydration if required.<br>• If fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) within 7 days, resume ITOVEBI at the same dose level.<br>• If fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) in ≥ 8 days, resume ITOVEBI at one lower dose level (see Table 1).<br>• If fasting glucose level > 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L) recurs within 30 days, interrupt ITOVEBI until fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L). Resume ITOVEBI at one lower dose level (see Table 1). |

| Adverse Reaction | Severity | Recommendation |
|---|---|---|
| | Fasting glucose level > 500 mg/dL (> 27.8 mmol/L) | • Interrupt ITOVEBI.<br>• Initiate or intensify anti-hyperglycemic medication[c,e].<br>• Assess for volume depletion and ketosis and administer appropriate hydration.<br>• If fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L), resume ITOVEBI at one lower dose level (see Table 1).<br>• If fasting glucose level > 500 mg/dL (> 27.8 mmol/L) recurs within 30 days, permanently discontinue ITOVEBI. |
| Stomatitis | Grade[f] 1 | • No adjustment of ITOVEBI required.<br>• Initiate or intensify appropriate medical therapy (e.g., corticosteroid-containing mouthwash) as clinically indicated. |
| | Grade[f] 2 | • Withhold ITOVEBI until recovery to Grade ≤ 1.<br>• Initiate or intensify appropriate medical therapy. Resume ITOVEBI at the same dose level.<br>• For recurrent Grade 2 stomatitis, withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at one lower dose level (see Table 1). |
| | Grade[f] 3 | • Withhold ITOVEBI until recovery to Grade ≤ 1.<br>• Initiate or intensify appropriate medical therapy. Resume ITOVEBI at one lower dose level (see Table 1). |
| | Grade[f] 4 | • Permanently discontinue ITOVEBI |
| Diarrhea | Grade[f] 1 | • No adjustment of ITOVEBI required. |

| Adverse Reaction | Severity | Recommendation |
|---|---|---|
| | | • Initiate appropriate medical therapy and monitor as clinically indicated. |
| | Grade [f] 2 | • Withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at the same dose level.<br>• Initiate or intensify appropriate medical therapy and monitor as clinically indicated.<br>• For recurrent Grade 2 diarrhea, withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at one lower dose level (see Table 1). |
| | Grade [f] 3 | • Withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at one lower dose level (see Table 1).<br>• Initiate or intensify appropriate medical therapy and monitor as clinically indicated. |
| | Grade [f] 4 | • Permanently discontinue ITOVEBI. |
| Hematologic toxicities | Grade[f] 1, 2, or 3 | • No adjustment of ITOVEBI required.<br>• Monitor complete blood count and for signs or symptoms of hematologic toxicities as clinically indicated. |
| | Grade [f] 4 | • Withhold ITOVEBI until recovery to Grade ≤ 2.<br>• Resume ITOVEBI at the same dose level or reduce to one lower dose level as clinically indicated (see Table 1). |
| Other Adverse Reactions[g] | Grade[f] 1 | • No adjustment of ITOVEBI required. |
| | Grade [f] 2 | • Consider interruption of ITOVEBI, if clinically indicated, until recovery to Grade ≤ 1.<br>• Resume ITOVEBI at the same dose level |
| | Grade [f] 3, first event | • Interrupt ITOVEBI until recovery to Grade ≤ 1. |

| Adverse Reaction | Severity | Recommendation |
|---|---|---|
| | | • Resume ITOVEBI at the same dose level or at one lower dose level based on clinical evaluation (see Table 1). |
| | Grade [f] 3, recurrent | • Interrupt ITOVEBI until recovery to Grade ≤ 1.<br>• Resume ITOVEBI at one lower dose level (see Table 1). |
| | Grade [f] 4 | • Permanently discontinue ITOVEBI. |

ULN = upper limit of normal

[a]Fasting glucose levels referenced in this table reflect hyperglycemia grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

[b] Before initiating treatment with ITOVEBI, fasting plasma glucose (FPG)/blood glucose (FBG) and $HbA_{1C}$ levels should be tested, and plasma/blood glucose levels should be optimized in all patients. After initiating treatment with ITOVEBI, patient fasting glucose (FPG or FBG) levels should be monitored or self-monitored based on the recommended schedule (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**Endocrine** and Metabolism). Metformin prophylaxis was recommended for patients with risk factors for hyperglycemia in the INAVO120 study (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperglycemia).

[c] Initiate applicable anti-hyperglycemic medications, such as metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, or insulin sensitizers (such as thiazolidinediones) or dipeptidyl peptidase-4 [DPP-4] inhibitors, and review the respective prescribing information for dosing and dose titration recommendations, including local hyperglycemia treatment guidelines. Metformin was recommended in the INAVO120 study as the preferred initial agent. See 8.2 Clinical Trial Adverse Reactions.

[d] Risk factors for hyperglycemia include, but are not limited to, (pre)diabetes, $HbA_{1C} \geq 5.7\%$, BMI ≥ 30 $kg/m^2$, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperglycemia).

[e] In the INAVO120 study, short-term insulin was allowed to control blood glucose levels when oral agents were inadequate, with the objective of returning to oral-only treatment after the acute episode resolved.

[f] Based on CTCAE version 5.0.

[g] For all grades: Initiate supportive therapy and monitor as clinically indicated.

*Pediatric Use (<18 years)*

Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (<18 years of age) and 10.3 Pharmacokinetics).

*Geriatric Use (≥65 years)*

No dose adjustment of ITOVEBI is recommended in patients ≥ 65 years of age. For details on geriatric data, see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (≥65 years of age) and 10.3 Pharmacokinetics.

*Renal Impairment*

No dose adjustment is recommended in patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min). The safety and efficacy of ITOVEBI have not been established in patients with moderate (eGFR ≥ 30 to < 60 mL/min based on CKD-EPI) or severe (< 30 mL/min based on CKD-EPI) renal impairment. The use of ITOVEBI is not recommended in patients with moderate or severe renal impairment (See 10.3 Pharmacokinetics, Renal Insufficiency).

*Hepatic Impairment*

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or AST > ULN and total bilirubin ≤ ULN). The safety and efficacy of ITOVEBI have not been studied in patients with moderate to severe hepatic impairment. For details on hepatic impairment data, see 10.3 Pharmacokinetics, Hepatic Insufficiency.

### 4.3 Administration

Advise patients to take ITOVEBI at approximately the same time each day.

Swallow ITOVEBI tablet(s) whole. Do not chew, crush, or split prior to swallowing.

### 4.4 Missed Dose

If a dose of ITOVEBI is missed, it can be taken within 9 hours after the time it is usually taken. After more than 9 hours, the dose should be skipped for that day. On the next day, ITOVEBI should be taken at the usual time.

If the patient vomits after taking the ITOVEBI dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

## 5 OVERDOSAGE

There is limited experience of overdose with ITOVEBI in clinical trials.

Patients who experience overdose should be closely supervised and supportive care instituted. There are no known antidotes for ITOVEBI.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 3: Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Oral | Tablets 3 mg and 9 mg inavolisib | Iron oxide red, iron oxide yellow*, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, purified water **, sodium starch glycolate, talc, titanium dioxide. |

*9 mg tablet only

**Removed during processing

ITOVEBI 3 mg film-coated tablet is red and round convex-shaped with an “INA 3” debossing on one side. Each 3 mg film-coated tablet contains 3 mg inavolisib.

ITOVEBI 9 mg film-coated tablet is pink and oval-shaped with an “INA 9” debossing on one side. Each 9 mg film-coated tablet contains 9 mg inavolisib.

*Packaging:*

*ITOVEBI 3 mg and 9 mg Blister Card*

Alu/alu (aluminum/aluminium) blister sealed into a blister card containing 7 film-coated tablets. Each carton contains 28 film-coated tablets (4 blister cards per carton).

## 7 WARNINGS AND PRECAUTIONS

### Dependence/Tolerance

There is no evidence that ITOVEBI has the potential for drug abuse or dependence.

### Driving and Operating Machinery

ITOVEBI has no or negligible influence on the ability to drive or use machines.

### Endocrine and Metabolism

***Hyperglycemia***: Severe hyperglycemia can occur in patients treated with ITOVEBI.

In the INAVO120 study, adverse reactions of hyperglycemia of any grade was reported in 60% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant; Grade 2 and Grade 3 events were reported in 38% and 6% of patients respectively.

In INAVO120, 46% (74/162) of patients who received ITOVEBI were treated with oral anti-hyperglycemic medications and 7% (11/162) were treated with insulin to manage increased fasting glucose. In patients who experienced increased fasting glucose of > 8.9 mmol/L, 96% (52/54) had an improvement in fasting glucose of at least one grade level with a median time to improvement from the first event of 8 days (range: 2 to 43 days).

Among patients with hyperglycemia, the median time to first onset was 7 days (range: 2 to 955 days). Hyperglycemia led to dose interruption in 28%, to dose reduction in 2.5%, and to discontinuation of ITOVEBI in 1.2% of patients.

The safety of ITOVEBI in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment have not been studied.

Before initiating treatment with ITOVEBI, test fasting glucose levels (FPG or FBG), $HbA_{1C}$ levels, and optimize fasting glucose (see Monitoring and Laboratory Tests). Patients should be advised of the signs

and symptoms of hyperglycemia (e.g., excessive thirst, urinating more often, blurred vision, mental confusion, difficulty breathing, or increased appetite with weight loss) and to immediately contact a healthcare professional if these symptoms occur. Optimal hydration should be maintained prior to and during treatment.

Anti-hyperglycemic treatment should be initiated or adjusted as required (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment). In patients with risk factors for hyperglycemia, metformin prophylaxis was allowed in the INAVO120 study. Therefore, metformin prophylaxis is similarly recommended for ITOVEBI in patients with risk factors for hyperglycemia.

Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycemic treatment and close monitoring of fasting glucose levels as clinically indicated.

Consultation with a healthcare professional experienced in the treatment of hyperglycemia, and initiation of fasting glucose monitoring at home should be considered for patients who have risk factors for hyperglycemia or who experience hyperglycemia.

Based on the severity of the hyperglycemia, ITOVEBI may require dose interruption, reduction, or discontinuation as described in

Table 2**Error! Reference source not found.** (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment). All patients should be instructed on lifestyle changes (e.g., dietary modifications, physical activity).

**Gastrointestinal**

**Stomatitis:** Severe cases of stomatitis can occur in patients treated with ITOVEBI.

Stomatitis occurred in 51% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant, including Grade 3 events in 6% of patients. The median time to first onset was 13 days (range: 1 to 610 days). Stomatitis led to interruption of ITOVEBI in 10%, to dose reduction in 3.7%, and to discontinuation of ITOVEBI in 0.6% of patients.

In patients who received ITOVEBI in combination with palbociclib and fulvestrant, 38% used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis.

Monitor patients for signs and symptoms of stomatitis. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

***Diarrhea:*** Severe diarrhea, including dehydration and acute kidney injury can occur in patients treated with ITOVEBI.

Diarrhea occurred in 48% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant, including Grade 2 events in 16.7%, and Grade 3 events in 3.7% of patients. The median time to first onset was 15 days (range: 2 to 602 days). Anti-diarrheal medicines were used in 28% (46/162) of patients who received ITOVEBI in combination with palbociclib and fulvestrant to manage symptoms. Dose interruptions were required in 7% of patients, and dose reductions occurred in 1.2% of patients.

Monitor patients for signs and symptoms of diarrhea. Advise patients to increase oral fluids and start antidiarrheal treatment at the first sign of diarrhea while taking ITOVEBI. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

**Monitoring and Laboratory Tests**

***Hyperglycemia***

Increased fasting glucose occurred in 85% of patients treated with ITOVEBI, including 22% of patients with Grade 2 (FPG > 8.9 to 13.9 mmol/L), 12% with Grade 3 (FPG > 13.9 to 27.8 mmol/L), and 0.6% with Grade 4 (FPG > 27.8 mmol/L) events according to CTCAE v4.03 (See
Table 6). Patients should be monitored for hyperglycemia (see Table 4).

**Table 4: Recommended Schedule for Monitoring Fasting Glucose and HbA1c Levels**

| | **Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with ITOVEBI** | **Recommended schedule for the monitoring of fasting glucose and HbA1c levels in patients with risk factors for hyperglycemia[a] treated with ITOVEBI** |
|---|---|---|
| At screening, before initiating treatment with ITOVEBI | Fasting glucose levels (FPG or FBG) and $HbA_{1C}$ levels should be tested, and fasting glucose levels should be optimized in all patients. | |
| After initiating treatment with ITOVEBI | Fasting glucose levels should be monitored or self-monitored<br>• once every 3 days for the first week (Day 1 to 7), then<br>• once every week for the next 3 weeks (Day 8 to 28), then<br>• once every 2 weeks for the next 8 weeks, then<br>• once every 4 weeks thereafter, and as clinically indicated.<br>$HbA_{1C}$ should be monitored every 3 months and as clinically indicated, according to the instructions of a healthcare professional. | Fasting glucose levels should be monitored or self-monitored daily as clinically indicated.<br>Metformin prophylaxis is recommended for patients with risk factors for hyperglycemia. |
| If a patient experiences hyperglycemia after initiating treatment with ITOVEBI | Fasting glucose levels should be monitored more closely as clinically indicated.<br>During treatment with anti-hyperglycemic medication, fasting glucose levels should continue to be monitored at least once a week for 8 weeks, followed by once every 2 weeks, and as clinically indicated. | |
| [a] Risk factors for hyperglycemia include, but not limited to, (pre)diabetes, $HbA_{1C} \geq 5.7\%$ , BMI ≥30 $kg/m^2$, ≥45 years of age, history of gestational diabetes, and family history of diabetes mellitus. | | |

**Renal**

ITOVEBI is known to be excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function.

**Reproductive Health**

***Fertility***

There are no clinical studies conducted to evaluate the effect of ITOVEBI on fertility. Based on animal studies, inavolisib may impact fertility in both females and males of reproductive potential (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental ToxicologyEndocrine and Metabolism).

***Contraception***

*Female*

Patients should be advised to use effective non-hormonal contraception during treatment with ITOVEBI and for 1 week after the last dose of ITOVEBI (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

*Male*

It is not known if ITOVEBI is present in semen. To avoid potential fetal exposure during pregnancy, male patients with female partners of childbearing potential or pregnant female partners should use effective contraception during treatment with ITOVEBI and for 1 week after the last dose of ITOVEBI.

***Pregnancy Testing***

The pregnancy status of females of reproductive potential should be verified prior to initiating ITOVEBI (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

### 7.1 7WARNINGS AND PRECAUTIONSSpecial Populations

### 7.2 Pregnancy

There are no clinical data available on the use of ITOVEBI during pregnancy. Based on animal studies and the mechanism of action, ITOVEBI is expected to cause harm to the developing fetus and/ or result in a loss of pregnancy. Studies in pregnant animals demonstrated that ITOVEBI lead to decreased fetal body and placental weight, post-implantation loss, fetal death, and teratogenicity (see 16 NON-CLINICAL TOXICOLOGY). Therefore, ITOVEBI should not be used during pregnancy.

If ITOVEBI is used during pregnancy or if a patient becomes pregnant while on treatment or a female is impregnated by a male partner being treated with ITOVEBI, the pregnant individual must be informed of the potential hazard to the fetus. Women of child bearing potential should avoid becoming pregnant by using effective non-hormonal contraception during treatment and for at least 1 week after the last dose of ITOVEBI.

Labour and Delivery

The use of ITOVEBI during labour and delivery has not been established.

### 7.3 Breast-feeding

It is not known whether inavolisib is excreted in human breast milk.

No studies have been conducted to assess the impact of inavolisib on milk production or its presence in breast milk. Because of the potential for serious adverse reactions in the breastfed infant, women should not breastfeed during ITOVEBI treatment and for 1 week after the last dose.

### 7.4 Pediatrics (<18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. The safety and efficacy of ITOVEBI in pediatric patients have not been established.

### 7.5 Geriatrics (≥65 years of age)

The safety and efficacy of ITOVEBI have been studied in geriatric patients up to 79 years of age. Of the 162 patients who received ITOVEBI in INAVO120, 14.8% were ≥ 65 years of age and 3% were ≥ 75 years of age.

Analysis of the safety of ITOVEBI comparing patients ≥ 65 years of age to younger patients suggest a higher incidence of ITOVEBI dosage modifications/interruptions (79.2% versus 68.1%).

Clinical studies of ITOVEBI did not include sufficient number of patients ≥ 65 years of age to assess whether there are differences in safety or efficacy.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The overall safety profile of ITOVEBI is based on data from 162 patients with locally advanced or metastatic breast cancer who received ITOVEBI in combination with palbociclib and fulvestrant in the INAVO120 Phase 3, randomized study. The median duration of ITOVEBI treatment at the time of the analysis was 9.2 months (range: 0 to 38.8 months).

The most common adverse reactions (ADRs) in patients treated with ITOVEBI in combination with palbociclib and fulvestrant (reported at a frequency ≥ 20%) were, hyperglycemia, stomatitis, diarrhea, thrombocytopenia, fatigue, anemia, nausea, rash, decreased appetite, and headache. Serious adverse events occurred in 24% of patients receiving ITOVEBI plus palbociclib and fulvestrant. Serious adverse reactions in ≥ 1% of patients receiving ITOVEBI plus palbociclib and fulvestrant included anemia (1.9%), diarrhea (1.2%), and urinary tract infection (1.2%).

Fatal adverse events occurred in 3.7% of patients who received ITOVEBI with palbociclib and fulvestrant, including (0.6% each) acute coronary syndrome, cerebral hemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal hemorrhage. None of the fatal adverse events were assessed as related to study treatment.

Adverse events led to permanent discontinuation of ITOVEBI in 6.2% of patients. The adverse events leading to discontinuation of ITOVEBI were hyperglycemia (1.2%), and (0.6% each) stomatitis, gastric ulcer, intestinal perforation, anal abscess, ALT increased, decreased weight, bone pain, musculoskeletal pain, transitional cell carcinoma, and acute kidney injury.

Adverse events led to dose interruptions of ITOVEBI in 69.1%% of patients, most frequently (≥ 2%) from hyperglycemia (28%), neutropenia (23%), COVID-19 infection (16%), stomatitis (10%), diarrhea (6.8%), thrombocytopenia (4.9%), anemia (4.3%), upper respiratory tract infection (4.3%), decreased white blood count (3.7%), pyrexia (3.1%), nausea (2.5%), and fatigue (2.5%).

Dose reductions of ITOVEBI due to adverse events occurred in 14% of patients. The most frequent adverse reactions leading to dose reduction of ITOVEBI in ≥ 2% of patients were stomatitis (3.7%) and hyperglycemia (2.5%).

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

*Tabulated summary of adverse drug reactions from clinical trials*

Adverse drug reactions from the INAVO120 study are listed by MedDRA system organ class in

Table 5. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (< 1/10,000).

**Table 5: Adverse Drug Reactions (≥10% with ≥ 5% (All Grades) or ≥ 2% (Grade 3-4) Higher Incidence in the ITOVEBI Arm in INAVO120**

| System Organ Class<br>Adverse Reaction | ITOVEBI + Palbociclib + Fulvestrant N=162 | | Placebo + Palbociclib + Fulvestrant N=162 | |
|---|---|---|---|---|
| | All Grades<br>n (%) | Grade 3-4<br>n (%) | All Grades<br>n (%) | Grade 3-4<br>n (%) |
| **Blood and Lymphatic System Disorders** | | | | |
| Thrombocytopenia[a] | 78 (48) | 23 (14) | 73 (45) | 7 (4) |
| Anemia[b] | 60 (37) | 10 (6)* | 59 (36) | 3 (2)* |
| **Gastrointestinal Disorders** | | | | |
| Stomatitis[c] | 83 (51) | 9 (6)* | 43 (27) | 0 |
| Diarrhea | 78 (48) | 6 (4)* | 26 (16) | 0 |
| Nausea | 45 (28) | 1 (1)* | 27 (17) | 0 |
| Vomiting | 24 (15) | 1 (1)* | 8 (5) | 2 (1)* |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue | 61 (38) | 3 (2)* | 41 (25) | 2 (1)* |
| **Infections and Infestations** | | | | |
| COVID-19 | 37 (23) | 3 (2) | 17 (11) | 1 (1) |
| Urinary Tract Infection | 21 (13) | 2 (1)* | 12 (7) | 0 |
| **Investigations** | | | | |
| Alanine aminotransferase increased | 28 (17) | 6 (4)* | 21 (13) | 2 (1)* |
| Weight decreased | 28 (17) | 6 (4)* | 1 (1) | 0 |
| **Metabolism and Nutrition Disorders** | | | | |
| Hyperglycemia[d] | 97 (60) | 9 (6)* | 16 (10) | 0 |
| Decreased appetite | 38 (24) | 0 | 14 (9) | 0 |
| Hypokalemia | 26 (16) | 4 (3) | 10 (6) | 0 |
| **Nervous System Disorders** | | | | |
| Headache | 34 (21) | 0 | 22 (14) | 0 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Rash[e] | 41 (25) | 0 | 28 (17) | 0 |
| Alopecia | 30 (19) | 0 | 9 (6) | 0 |
| Dry skin[f] | 21 (13) | 0 | 7 (4) | 0 |

Grading according to CTCAE version 5.0.

* No Grade 4 events were observed.

[a] Includes platelet count decreased and thrombocytopenia.

[b] Includes anemia and hemoglobin decreased.

| System Organ Class<br>Adverse Reaction | ITOVEBI + Palbociclib + Fulvestrant N=162 | | Placebo + Palbociclib + Fulvestrant N=162 | |
|---|---|---|---|---|
| | All Grades<br>n (%) | Grade 3-4<br>n (%) | All Grades<br>n (%) | Grade 3-4<br>n (%) |
| [c] Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis. | | | | |
| [d] Includes hyperglycemia, blood glucose increased, hyperglycemic crisis, glycated serum protein increased, glucose tolerance impaired, diabetes mellitus, Type 2 diabetes mellitus, and glycosylated hemoglobin increased. | | | | |
| [e] Includes dermatitis, dermatitis acneiform, dermatitis bullous, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, and rash pustular. | | | | |
| [f] Includes dry skin, skin fissures, xerosis, and xeroderma. | | | | |

In

Table 5 in addition to hyperglycemia, stomatitis, and diarrhea, an increase in Grade 3-4 adverse events with the addition of ITOVEBI to the combination of palbociclib and fulvestrant occurred in the following adverse drug reactions: urinary tract infection, thrombocytopenia, anemia, hypokalemia, nausea, fatigue, alanine aminotransferase increased, and weight decreased.

### 8.3 Less Common Clinical Trial Adverse Reactions

Other clinically relevant adverse reactions occurring in <10% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant or with < 5% (all grades) or < 2% (Grade 3-4) greater incidence in the ITOVEBI arm than the placebo arm are presented below:

**Metabolism and Nutrition Disorders**: Hypocalcemia (all grades: 9%; Grade 3: 1%; no Grade 4 events).

**Eye Disorders**: Dry eye (all grades: 9%; Grade 3-4: 0%).

**Gastrointestinal Disorders:** Abdominal pain, including abdominal pain, abdominal pain upper, abdominal pain lower (all grades: 15%; Grade 3: 1%; no Grade 4 events); dysgeusia, including dysgeusia, ageusia, and hypogeusia (all grades: 9%; Grade 3-4: 0%); dyspepsia (all grades: 8%; Grade 3-4: 0%)

**Investigations:** Blood insulin increased (all grades: 6%; Grade 3-4: 0%)

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

The following table summarizes treatment-emergent shifts from baseline in laboratory abnormalities in the INAVO120 study.

**Table 6: Laboratory Abnormalities with a ≥ 2% (All Grades or Grade 3-4) Higher Incidence in the ITOVEBI Arm in INAVO120**

| Laboratory Abnormality | ITOVEBI + Palbociclib + Fulvestrant[a] | | Placebo + Palbociclib + Fulvestrant[b] | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3-4 (%) | All Grades (%) | Grade 3-4 (%) |
| **Hematology** | | | | |
| Glucose (fasting) increased[c] | 85.4 | 12.1 | 42.9 | 0 |
| Hemoglobin decreased | 87.5 | 7.5* | 85.1 | 2.5* |
| Lymphocytes (absolute) decreased | 72.1 | 9 | 68.2 | 14.4 |
| Neutrophils (total, absolute) decreased | 95.1 | 82 | 97 | 78.8 |
| Platelets decreased | 83.8 | 15.6 | 71.4 | 3.7 |
| **Chemistry** | | | | |
| ALT increased | 34.4 | 3.1* | 28.6 | 1.2* |
| Albumin decreased | 25 | 0.6* | 18.1 | 0 |

| Laboratory Abnormality | ITOVEBI + Palbociclib + Fulvestrant[a] | | Placebo + Palbociclib + Fulvestrant[b] | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3-4 (%) | All Grades (%) | Grade 3-4 (%) |
| Calcium decreased | 41.9 | 3.1 | 31.7 | 3.7 |
| Creatinine increased | 37.5 | 1.9* | 29.8 | 1.2* |
| Glucose (fasting) decreased[c] | 6.4 | 0 | 3.2 | 0 |
| Lipase (fasting) increased | 16 | 1.4* | 6.9 | 0 |
| Magnesium decreased | 26.9 | 0.6 | 20.5 | 0 |
| Potassium decreased | 37.5 | 6.2 | 20.5 | 0.6* |
| Sodium decreased | 27.5 | 2.5* | 18.6 | 2.5 |

ALT = alanine aminotransferase

*No Grade 4 events were observed.

[a] The denominator used to calculate the rate varied from 122 to 160 based on the number of patients with a baseline value and at least one post-treatment value.

[b] The denominator used to calculate the rate varied from 131 to 161 based on the number of patients with a baseline value and at least one post-treatment value.

[c] Grading according to CTCAE version 4.03.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

Clinical study results show that the predominant metabolites of inavolisib are not mediated by CYP enzymes, suggesting a low likelihood of interaction between inavolisib and CYP inhibitors or inducers.

Inavolisib is a time-dependent inhibitor and an inducer of CYP3A. It is also an inducer of CYP2B6.

Inavolisib is a substrate of P-gp and BCRP.

### 9.3 Drug-Behavioural Interactions

There are no drug-behavioural interactions known at this time.

### 9.4 Drug-Drug Interactions

No pharmacokinetic drug-drug interaction clinical studies have been conducted with inavolisib.

**Effects of inavolisib on other drugs**

*CYP Substrates*

*In vitro* studies show that inavolisib is a time-dependent inhibitor and an inducer of CYP3A. It is also an inducer of CYP2B6. Inavolisib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 and does not induce CYP1A2 at clinically relevant concentrations.

*Transporters*

*In vitro* studies have shown that inavolisib does not appear to have the potential to inhibit any of the transporters tested (P-glycoprotein [P-gp], breast cancer resistance protein [BCRP], OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2K, OAT1, or OAT3) at clinically relevant concentrations.

**Effects of other drugs on inavolisib**

*Transporters*

*In vitro* studies have shown that inavolisib is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT3, OAT1, MATE1, or MATE2K, but is a substrate of P-gp and BCRP.

### 9.5 Drug-Food Interactions

No clinically meaningful effect of food on inavolisib exposure was observed in a clinical study.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Inavolisib is a selective inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) with activity predominantly against the catalytic subunit alpha isoform protein (p110α; encoded by the *PIK3CA* gene). In vitro, inavolisib lead to the degradation of mutated p110α, inhibited the activity of downstream PI3K pathway target, AKT, reduced cellular proliferation and induction of apoptosis in *PIK3CA*-mutated breast cancer cell lines. In *PIK3CA*-mutated breast cancer xenograft models, inavolisib reduced tumor growth, which increased when combined with the CDK4/6 inhibitor palbociclib and the endocrine therapy fulvestrant, as compared to any treatment alone or in doublet combinations.

### 10.2 Pharmacodynamics

*Exposure-Response Relationships*

The exposure-response relationship for the efficacy of inavolisib has not been fully characterized.

Higher systemic exposure of inavolisib was associated with higher incidence of Grade ≥ 2 anemia, Grade ≥ 2 hyperglycemia, and inavolisib dose modification due to adverse event.

*Cardiac Electrophysiology*

The ability of inavolisib to prolong the QT interval was assessed in a pharmacokinetic-pharmacodynamic analysis of 172 patients with locally advanced or metastatic *PIK3CA*-mutated solid tumours given 3 mg to 12 mg once daily dosing of inavolisib in an open-label, multi-arm uncontrolled study. At the recommended ITOVEBI dose, a mean increase in the QTc interval of > 20 ms is unlikely.

### 10.3 Pharmacokinetics

The pharmacokinetics of inavolisib were characterized in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumors, including breast cancer, under an oral dosing regimen ranging from 3 mg to 12 mg daily and in healthy subjects at 9 mg single dose.

Inavolisib pharmacokinetics are presented as geometric mean (geometric coefficient of variation [geo CV]%) following administration of the approved recommended dosage unless otherwise specified. The inavolisib steady-state AUC is 1,010 h*ng/mL (25%) and $C_{max}$ is 69 ng/mL (27%). Inavolisib exhibited dose-proportional pharmacokinetics (steady-state $AUC_{0-24}$ is proportional with dose) in patients with locally advanced or metastatic breast cancer over a dose range of 6 mg to 12 mg (0.7 to 1.3 times the recommended dose). Steady-state concentrations are predicted to be attained by day 5.

**Table 7: Summary of Inavolisib Pharmacokinetic Parameters in Patients with Locally Advanced or Metastatic Breast Cancer**

| PK Parameter | **Steady State $C_{max}$ (ng/mL)** | **Steady State $T_{max}$ (h)** | **Single dose $t_{½}$ (h)** | **Steady State $AUC_{0-\tau}$ (h*ng/mL)** | **CL (L/hr)** | **Vd (L)** |
|---|---|---|---|---|---|---|
| **Geometric Mean (Geo CV%)** | 69 (27%) | 3 (0.5 to 4) | 15 (22%) | 1,010 (25%) | 8.83 (29%) | 155 (26%) |

Parameters are presented as geometric mean values [geometric coefficient of variation (geo CV)%] or median (min to max) for $T_{max}$.

$AUC_{0-\tau}$: area under the curve from time zero to τ (τ = 24 hour for Inavolisib); $C_{max}$: maximum concentration; $t_{½}$: terminal half-life; $T_{max}$: time to reach $C_{max}$; $V_d$: apparent (oral) volume of distribution; CL: clearance

Parameters presented are derived using the population pharmacokinetics modelling except for the steady state $T_{max}$ which is based on observed non-compartmental analysis.

**Absorption:**

The time to maximum plasma concentration ($T_{max}$) was reached after a median of 3 hours (range: 0.5 to 4 hours) at steady state following 9 mg once daily dosing of inavolisib, under fasted conditions.

With 9 mg once daily dosing, the geometric mean accumulation ratio was 2.04.

The absolute bioavailability of inavolisib was 76%.

No clinically significant effect of food on inavolisib exposure was observed.

**Distribution:**

Plasma protein binding of inavolisib was 37% bound and did not appear to be concentration-dependent over the concentration range tested (0.1 - 10 µM). In humans, the estimated apparent (oral) volume of distribution is 155 L (26%) and the blood-to-plasma ratio is 0.794.

**Metabolism:**

Minimal metabolism of inavolisib was detected *in vitro* in human liver microsome incubations. This minimal oxidative metabolism appeared to be mediated by CYP3A4/5.

Following oral administration of a single radiolabeled 9 mg dose of inavolisib to healthy subjects, parent drug was the most prominent drug-related compound in plasma and urine. Total metabolites in the excreta accounted for 42% (35% in feces and 7% in urine) of the dose. Hydrolysis was the major metabolic pathway with no oxidative metabolites detected in plasma and representing approximately 2% of the dose in urine and feces.

**Elimination**

Following oral administration of a single radiolabeled 9 mg dose of inavolisib to healthy subjects, 48.5% of the administered dose was recovered in urine (40.4% unchanged) and 48% in feces (10.8% unchanged).

In clinical studies, the geometric mean of the individual elimination half-life estimate for inavolisib was 15 hours (22%) following a single 9 mg dose. The estimated total clearance of inavolisib is 8.83 L/hr (29%).

**Special Populations and Conditions**

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. No studies have been conducted to investigate the pharmacokinetics of inavolisib in pediatric patients.
- **Geriatrics:** No clinically significant differences in inavolisib pharmacokinetics were noted between patients 65 years of age and older and those under 65 years based on population pharmacokinetic analysis.
- **Ethnic origin:** No clinically significant differences in inavolisib pharmacokinetics were noted based on the covariate of race (Asian or all others, with the majority Caucasian) according to population pharmacokinetic analysis.
- **Hepatic Insufficiency:** Population pharmacokinetic analyses indicated that mild hepatic

impairment is not a significant covariate on inavolisib exposure. The pharmacokinetics of inavolisib in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or AST > ULN and total bilirubin ≤ ULN) were similar to those in patients with normal hepatic function. The effect of moderate (AST any value and total bilirubin 1.5-3.0 ULN) to severe (AST any value and total bilirubin > 3.0 ULN) hepatic impairment on inavolisib pharmacokinetics has not been studied.

- **Renal Insufficiency:** Population pharmacokinetic analyses indicated that mild renal impairment is not a significant covariate on inavolisib exposure. The pharmacokinetics of inavolisib in patients with mild renal impairment (eGFR ≥60 to < 90 mL/min) were similar to those in patients with normal renal function. The effect of moderate (eGFR ≥ 30 to < 60 mL/min based on CKD-EPI) and severe (eGFR < 30 mL/min) renal impairment on ITOVEBI pharmacokinetics has not been established. The use of ITOVEBI is not recommended in patients with moderate or severe renal impairment (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, *Renal Impairment*).
- **Obesity:** No clinically significant differences in inavolisib pharmacokinetics were noted based on body weight (39 to 159 kg) according to population pharmacokinetic analysis.

## 11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature, 15°C to 30°C.

*Renal Impairment*

Blister: This medicine should not be used after the expiry date (EXP) shown on the blister packaging.

## 12 SPECIAL HANDLING INSTRUCTIONS

Disposal of Unused/Expired Medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**PART II: SCIENTIFIC INFORMATION**

## 13 PHARMACEUTICAL INFORMATION

### Drug Substance

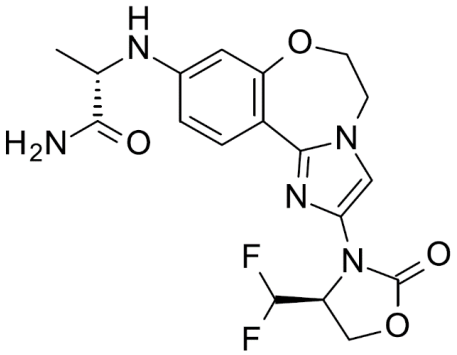
Proper/ Common name: inavolisib

Chemical name: (2S)-2-[[2-[(4S)-4-(difluoromethyl)-2-oxo-oxazolidin-3-yl]-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]amino]propanamide

Molecular formula and molecular mass: $C_{18}H_{19}F_2N_5O_4$.

407.37 g/mol, 407.37 ($M_r$) (free form)

Structural formula:



Physicochemical properties: White to off-white, greyish pink, greyish orange, or greyish yellow powder or powder with lumps

At lower pH-values, solubility of inavolisib increases. At pH 1, the solubility increases with time and equilibrium is not reached within the first 4 hour.

| Aqueous Media or Buffer | pH Medium | pH, 24 h | Solubility at 37°C, 4 h (mg/mL) | Solubility at 37°C, 24 h (mg/mL) |
|---|---|---|---|---|
| 0.1 N HCl | 1.09 | 1.17 | 2.41 | 8.14 |
| 50 mM Acetate Buffer | 4.50 | 4.47 | 0.06 | 0.05 |
| 50 mM Phosphate Buffer | 6.80 | 6.78 | 0.05 | 0.04 |

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

**Locally Advanced or Metastatic Breast Cancer**

***INAVO120***

**Study Demographics and Trial Design**

**Table 8: Summary of Patient Demographics for INAVO120 in Locally Advanced or Metastatic Breast Cancer Patients**

| Study # | Study Design | Dosage, route of administration and duration | Study subjects (n) | Median age (Range) | Sex n (%) |
|---|---|---|---|---|---|
| INAVO120 | Phase III, randomized, double-blind, placebo-controlled | ITOVEBI 9 mg/placebo QD PO + palbociclib 125 mg QD PO (21/7) + fulvestrant 500 mg Q4W IM (Days 0 and 14 of first 28-day cycle, and then Day 0 of each following 28-day cycle)<br><br>Until PD or unacceptable toxicity | Total: N = 325<br><br>ITOVEBI + Palbo + Fulv: N = 161<br><br>Pbo+Palbo+Fulv: N = 164 | 54 years (range:<br><br>27-79) | F: 319 (98.2)<br><br>M: 6 (1.8) |
| Fulv= fulvestrant; IM = intramuscular; Palbo = palbociclib; PD = progressive disease; PO = per oral; QD = once daily; Q4W = every 4 weeks. | | | | | |

The efficacy of ITOVEBI in combination with palbociclib and fulvestrant was evaluated in a Phase III, randomized, double-blind, placebo-controlled study in adult patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. The study excluded patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing systemic therapy at the start of study treatment.

*PIK3CA* mutation status was prospectively determined through testing of plasma-derived circulating tumour DNA (ctDNA) using a next-generation sequencing (NGS) assay at a central laboratory, or in local

laboratories using various validated polymerase chain reaction (PCR) or NGS assays on tumor tissue or plasma.

A total of 325 patients were randomized 1:1 to receive either ITOVEBI 9 mg (n=161) or placebo (n=164) orally once daily, in combination with palbociclib and fulvestrant, until disease progression or unacceptable toxicity. In addition, pre/perimenopausal women and men received an LHRH agonist throughout therapy. Randomization was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

The baseline demographic and disease characteristics were: median age 54 years (range: 27 to 79 years); 98.2% female, of which 38.2% were pre/perimenopausal; 58.8% White, 38.2% Asian, 2.5% unknown, 0.6% Black or African American; 6.2% Hispanic or Latino; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 (63.4%) or 1 (36.3%). Tamoxifen (56.9%) and aromatase inhibitors (50.2%) were the most commonly used adjuvant endocrine therapies. The demographics and baseline disease characteristics were balanced and comparable between study arms.

The primary efficacy outcome measure was investigator (INV)-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The secondary efficacy outcome measures included overall survival (OS), objective response rate (ORR), and duration of response (DOR).

***INAVO120***

**Study Results**

Efficacy results are summarized in Table 9, and Figure 1**Error! Reference source not found.**. INV-assessed PFS results were supported by consistent results from blinded independent central review (BICR) assessment.

**Table 9**: **Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120**

| **Efficacy Endpoint** | **ITOVEBI + Palbociclib + Fulvestrant N=161** | **Placebo + Palbociclib + Fulvestrant N=164** |
|---|---|---|
| ***Primary Endpoint*** | | |
| **INV-Assessed Progression-Free Survival[a]** | | |
| Patients with event, n (%) | 82 (50.9) | 113 (68.9) |
| Median, months (95% CI) | 15 (11.3, 20.5) | 7.3 (5.6, 9.3) |
| Hazard ratio (95% CI) | 0.43 (0.32, 0.59) | |

| Efficacy Endpoint | ITOVEBI + Palbociclib + Fulvestrant N=161 | Placebo + Palbociclib + Fulvestrant N=164 |
|---|---|---|
| p-value | < 0.0001 | |
| ***Secondary Endpoints*** | | |
| **Overall Survival**[b] | | |
| Patients with event, n (%) | 42 (26.1) | 55 (33.5) |
| Median, months (95% CI) | NE (27.3, NE) | 31.1 (22.3, NE) |
| Hazard ratio (95% CI) | 0.64 (0.43, 0.97) | |
| p-value | 0.0338 | |
| **Objective Response Rate**[a,c] | | |
| Patients with CR or PR, n (%) | 94 (58.4) | 41 (25) |
| 95% CI | (50.4, 66.1) | (18.6, 32.3) |
| **Duration of Response** | | |
| Median DOR, months (95% CI) | 18.4 (10.4, 22.2) | 9.6 (7.4, 16.6) |

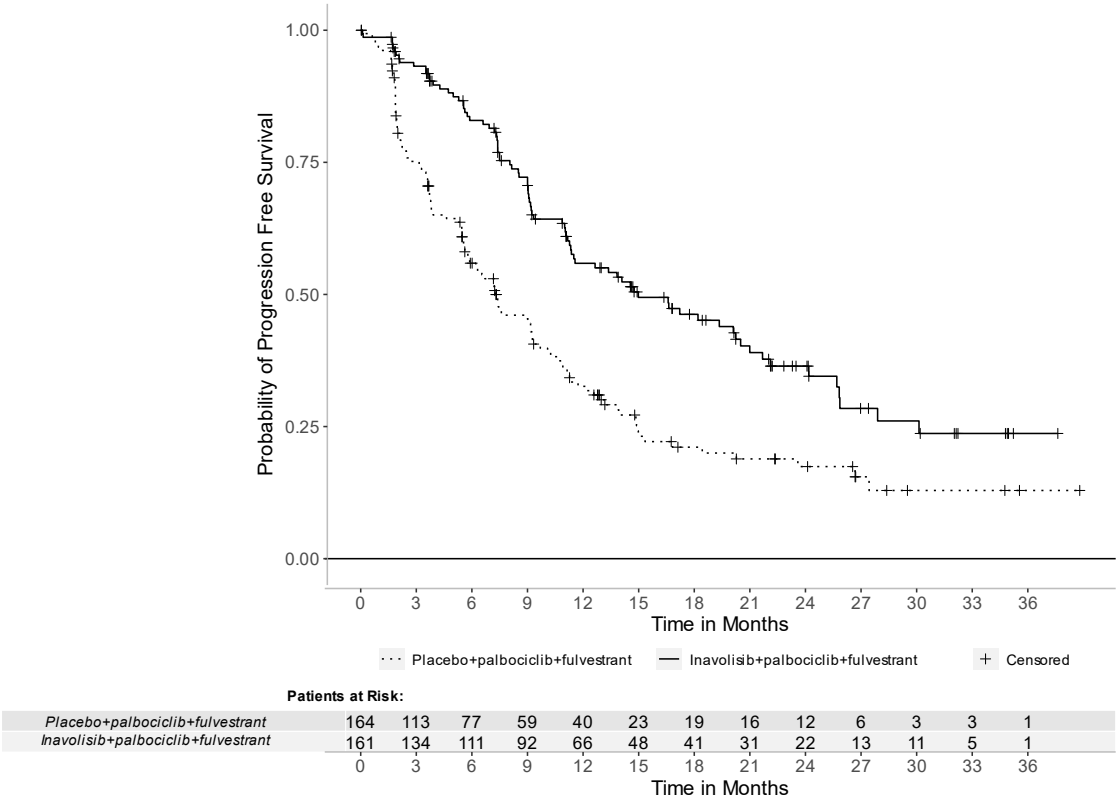
CI = confidence interval; CR = complete response; NE = not evaluable; PR = partial response

[a] Per RECIST version 1.1.

[b] Based on interim analysis. Under the interim analysis stopping boundary ($p \leq 0.0098$), statistical significance was not reached.

[c] ORR is defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator.

**Figure 1**: **INV-Assessed Progression-Free Survival in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120**




The study met its primary endpoint of (INV)-assessed PFS. Addition of ITOVEBI to the combination of palbociclib and fulvestrant demonstrated a statistically significant improvement in median PFS, by reducing the risk of disease progression or death by 57% in patients with *PIK3CA*-mutated, HR-positive, HER2-negative LA/mBC (Stratified hazard ratio [HR] = 0.43 [95% CI: 0.32, 0.59], p<0.0001). Prespecified PFS analyses per investigator assessment showed a generally consistent treatment effect in favour of the ITOVEBI arm in patient subgroups including age, sex, ethnicity, race, ECOG performance status, menopausal status, presence of visceral disease (yes or no), presence of liver metastases (yes or no), number of metastatic organ sites, and endocrine resistance (primary or secondary). At interim analysis, while the key secondary endpoint, OS, was not statistically significant, it is supportive of the primary endpoint.

*Patient-Reported Outcomes*

Patients reported on seven selected symptomatic toxicities (diarrhea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash) via the Patient-Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE) corresponding to the known, reportable side effects of ITOVEBI, palbociclib, and fulvestrant, as well as their overall level of bother due to treatment side effects via a single item/question.

Completion rates in both arms were > 90% at baseline and > 80% at subsequent time points where > 50% of randomized patients were on treatment.

In both arms, worst post-baseline levels of 'moderate'/'somewhat' or less were reported by > 70% of patients for decreased appetite, nausea, and vomiting, and by > 60% of patients for mouth sores, diarrhea, and fatigue. Greater proportions of patients in the ITOVEBI arm reported post-baseline symptomatic toxicities at 'severe'/'frequently' or 'very severe'/'almost constantly' levels; these differences were greatest for mouth sores, decreased appetite, and diarrhea (Table 10). Rash was reported in 53.9% and 40.5% of patients in the ITOVEBI and placebo arms, respectively, post-baseline.

**Table 10**: **Proportion of Patients Reporting Worst Post-baseline Levels of PRO-CTCAE Symptoms Items in INAVO120**

| **Symptom (Attribute)[a]** | **Baseline Score ≤ 1[a]** | | **Post-baseline Score ≤ 2[a]** | | **Post-baseline Score ≥ 3[a]** | |
|---|---|---|---|---|---|---|
| | **Inavo+P+F (N=148)** | **Pbo+P+F (N=152)** | **Inavo+P+F (N=152)** | **Pbo+P+F (N=158)** | **Inavo+P+F (N=152)** | **Pbo+P+F (N=158)** |
| Mouth sores (severity), % | 97.3 | 97.4 | 69.7 | 91.1 | 30.2 | 8.9 |
| Decreased appetite (severity), % | 89.9 | 91.5 | 73 | 87.4 | 27 | 12.7 |
| Nausea (frequency), % | 89.2 | 91.4 | 80.3 | 86.7 | 19.7 | 13.3 |
| Vomiting (frequency), % | 95.9 | 98 | 94.1 | 96.8 | 5.9 | 3.2 |
| Diarrhea (frequency), % | 91.2 | 93.5 | 67.1 | 89.9 | 32.9 | 10.1 |
| Fatigue (severity), % | 73.6 | 73 | 63.2 | 72.8 | 36.8 | 27.2 |

| **Symptom (Attribute)** | **Baseline Presence** | | **Post-baseline Presence** | |
|---|---|---|---|---|
| | **Inavo+P+F (N=148)** | **Pbo+P+F (N=152)** | **Inavo+P+F (N=152)** | **Pbo+P+F (N=158)** |
| Rash (yes/no), % | 94.6 (No) | 95.4 (No) | 53.9 (Yes) | 40.5 (Yes) |

| Symptom (Attribute)[a] | Baseline Score ≤ 1[a] | Post-baseline Score ≤ 2[a] | Post-baseline Score ≥ 3[a] |
|---|---|---|---|
| Inavo+P+F = Itovebi plus palbociclib and fulvestrant arm; N/A = not applicable; Pbo+P+F = placebo plus palbociclib and fulvestrant arm<br>[a] The symptom attribute scoring is defined by amount/frequency/severity with a score of 0 = 'not at all'/'never'/'none'; 1 = 'a little bit'/'rarely'/'mild'; 2 = 'somewhat'/'occasionally'/'moderate'; 3 = 'quite a bit'/'frequently'/'severe'; 4 = 'very much'/'almost constantly'/'very severe'. | | | |

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology

The key inavolisib effects observed in repeat dose toxicity studies included hyperglycemia and body weight loss in rats and dogs, inflammation in dogs, bone marrow hypocellularity, atrophy of glandular and reproductive tissues, eye lens degeneration in rats, lymphoid depletion, and lens fiber swelling and lens cortex vacuolation in the eye in dogs. The NOAEL were 1.5 mg/kg/day and 0.3 mg/kg/day in rats and dogs, respectively, which corresponds to 0.44 times and 0.56 times the human exposure at a clinical dose of 9 mg.

Findings were generally dose-dependent and reversible, considered to be clinically monitorable and/or manageable. Lens fiber swelling and lens vacuolation in dogs (at ≥ 0.56 times the human exposure at a clinical dose of 9 mg) were reversible. Lens fiber degeneration observed in rats (at ≥ 3.6 times the human exposure at a clinical dose of 9 mg) was considered irreversible.

### Carcinogenicity

No carcinogenicity studies with inavolisib have been conducted.

### Genotoxicity

Inavolisib was not mutagenic in the bacterial mutagenesis assay.

Inavolisib showed clastogenicity in an *in vitro assay in human lymphocytes*; however, there was no evidence of inavolisib induced *in vivo* genotoxicity (clastogenicity, aneugenicity, or DNA damage) in the micronucleus and comet study in rats at doses up to a maximum tolerated dose (MTD) of 16.1 times the human exposure at a clinical dose of 9 mg.

### Reproductive and Developmental Toxicology

An embryo-fetal development study in Sprague Dawley rats identified inavolisib-related dose dependent effects on embryo-fetal development (at ≥ 0.8 times the human exposure at a clinical dose of 9 mg) that included decreases in fetal body weight and placental weight, post-implantation loss, lower fetal viability, and teratogenicity (fetal external, visceral, and skeletal malformations including edema, anasarca, absent eye bulge, microphthalmia, fused thoracic arch, and kyphosis of the vertebral column).

No dedicated fertility studies with inavolisib have been conducted.

In male rats, dose-dependent atrophy of the prostate and seminal vesicle and decreased organ weights without microscopic correlate in the epididymis and testis were observed (at ≥ 0.4 times the human exposure at a clinical dose of 9 mg). In the 1-month toxicity study in dogs, focal inspissation of seminiferous tubule contents, multinucleated spermatids in the testis, and epithelial degeneration/necrosis in the epididymis were observed (at ≥ 2 times the human exposure at a clinical dose of 9 mg). Multinucleated spermatids in the testis persisted through the 4-week recovery period. However, there were no inavolisib-related microscopic findings in the testes or epididymides or effects on sperm concentration, motility, or morphology in the 3-month dog toxicity study at similar exposures.

In female rats, minimal to mild and reversible atrophy in the uterus and vagina and decreased ovarian follicles were observed (at ≥ 1.1 times the human exposure at a clinical dose of 9 mg) in the 4-week toxicity study. Findings suggestive of an interruption/alteration of the estrus cycle were observed (at ≥ 1.5 times the human exposure at a clinical dose of 9 mg) in the 3-month rat toxicity study.

**Special Toxicology**

Inavolisib did not show phototoxicity potential in the *in vitro* BALB/c 3T3 mouse fibroblast assay.

## Patient Medication Information

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrITOVEBI®**

**inavolisib tablets**

Read this carefully before you start taking **ITOVEBI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ITOVEBI**.

### Serious warnings and precautions box

ITOVEBI can cause serious side effects including:

- **Hyperglycemia** (high blood sugar). Your healthcare professional will test your blood sugar levels before and during treatment with ITOVEBI. Stay well-hydrated before and during treatment with ITOVEBI. Your healthcare professional will monitor your blood sugar levels and treat you as needed. They may treat you with a medicine called metformin.

  See the "**Serious side effects and what to do about them**" table, below, for more information on these and other serious side effects.

### What ITOVEBI is used for:

ITOVEBI is used with palbociclib and fulvestrant to treat breast cancer in adults. The breast cancer:

- is endocrine-resistant (has come back while the patient is receiving, or after the patient has completed hormonal treatment),
- is HR-positive (hormone receptor-positive),
- is HER2-negative (human epidermal growth factor receptor 2-negative),
- has a change (mutation) in a gene called '*PIK3CA*', and
- has spread to nearby tissue or lymph nodes, or other parts of the body.

Before taking ITOVEBI, a test will be performed. This is to confirm if ITOVEBI is right for you.

### How ITOVEBI works:

ITOVEBI works by blocking the effects of a protein that is made by the mutated *PIK3CA* gene. This helps destroy cancer cells, and slows the growth and spread of the cancer.

### The ingredients in ITOVEBI are:

Medicinal ingredients: inavolisib

Non-medicinal ingredients: iron oxide red, iron oxide yellow (9 mg tablet only), lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, purified water, sodium starch glycolate, talc, titanium dioxide

**ITOVEBI comes in the following dosage forms:**

Tablet: 3 mg & 9 mg

- Each 3 mg tablet contains 3 mg inavolisib.
- Each 9 mg tablet contains 9 mg inavolisib.

**Do not use ITOVEBI if:**

- you are allergic to inavolisib or any of the other ingredients of ITOVEBI or the container.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ITOVEBI. Talk about any health conditions or problems you may have, including if you:**

- are pregnant or plan to become pregnant. ITOVEBI can harm your unborn baby,
- have kidney problems,
- have or had high blood sugar levels, diabetes, gestational diabetes, a family history of diabetes,
- are 65 years of age or older.

**Other warnings you should know about:**

**Stomatitis** (mouth sores, redness and swelling of the lining of the mouth): ITOVEBI can cause stomatitis. Your healthcare professional will monitor you for signs and symptoms of stomatitis. They will treat you as needed.

**Diarrhea**: ITOVEBI can cause severe diarrhea. This can lead to dehydration and kidney problems. Your healthcare professional will monitor your electrolyte levels and treat you as needed.

See the "**Serious side effects and what to do about them**" table, below, for more information on these and other serious side effects.

**Blood Tests for Hyperglycemia (high blood sugar):**

- Your healthcare professional will do blood tests before, during and after treatment with ITOVEBI. This is to check your blood health and blood sugar levels.
- Your healthcare professional may also ask you to check your blood sugar at home. They will tell you exactly how and when to test your blood sugar.
    - Always follow your healthcare professional's exact instructions for checking blood sugar levels. This helps detect if you have high blood sugar early.
- Your healthcare professional will tell you if your blood sugar levels are abnormal and if you need treatment. Treatment can include medicines or lifestyle changes like diet and exercise.

**Pregnancy and Breastfeeding:**

- If you are pregnant, able to get pregnant, or planning on having a baby, there are risks you should discuss with your healthcare professional.
- You should not take ITOVEBI if you are pregnant. It may harm your unborn baby.
- Your healthcare professional may do a pregnancy test before you start taking ITOVEBI. This test must show you are not pregnant.

- If you think you are pregnant, become pregnant while taking ITOVEBI, or become pregnant by your male partner who is taking ITOVEBI, tell your healthcare professional right away.
- You should not breast-feed while taking ITOVEBI and for 1 week after your last dose.

**Birth Control for Females and Males:**

- **Females:** Use a non-hormonal method of birth control during treatment and for 1 week after your last dose. Ask your healthcare professional about birth control that is right for you.
- **Males:** Use effective birth control each time you have sex with a woman who is pregnant, may be pregnant or could get pregnant. Keep using effective birth control until 1 week after your last dose. Ask your healthcare professional about birth control that is right for you.
    - If, during your treatment with ITOVEBI, your sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.

**Fertility for Females and Males**:

- Treatment with ITOVEBI may affect your ability to have or father a child. If you have questions about this, talk to your healthcare professional.

**Children and Adolescents:**

- ITOVEBI is not for children and adolescents under 18 years old.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**How to take ITOVEBI:**

- Always take this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take ITOVEBI with or without food, at the same time each day.
- Swallow tablets whole. Do not chew, crush or split tablets.
- Take ITOVEBI for as long as your healthcare professional prescribes it. Do not stop taking this medicine unless your healthcare professional tells you to.

**Usual dose:**

**Adults:** Take exactly as directed. Your healthcare professional will decide on the right dose for you.

- Your healthcare professional may lower your dose, stop treatment for a period of time, or stop treatment completely. This may happen if you experience serious side effects.
- You will also receive treatment with palbociclib and fulvestrant. Your healthcare professional will determine your dose and schedule.

**Overdose:**

If you think you, or a person you are caring for, have taken too much ITOVEBI, contact a healthcare professional, hospital emergency department, or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

**Missed Dose:**

- If you miss a dose of ITOVEBI, you may still take it up to 9 hours after the time you should have taken it.
- If it has been more than 9 hours from the time you should have taken it, skip the dose for that day. The next day, take the dose at your usual time.
- Do not take an extra dose to make up for the one that you missed.
- If you vomit after taking a dose of ITOVEBI, do not take an extra dose on that day. Take your regular dose of ITOVEBI at your usual time the next day.

**What are possible side effects from using ITOVEBI?**

These are not all the possible side effects you may have when taking ITOVEBI. If you experience any side effects not listed here, tell your healthcare professional.

- Diarrhea
- Tiredness
- Feeling sick to your stomach (nausea), vomiting
- Rash
- Dry skin
- Loss of appetite
- Headache
- Hair loss or hair thinning
- Weight loss
- Abdominal pain
- Dry eyes
- Upset stomach or indigestion
- Changes in the way food tastes or lost sense of taste
- COVID-19 infection or cold symptoms

ITOVEBI can cause abnormal blood test results. Your healthcare professional will do blood tests before, during and after your treatment. These will tell your healthcare professional how ITOVEBI is affecting your blood.

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **VERY COMMON** | | | |
| **Hyperglycemia** (high blood sugar): difficulty breathing, confusion, nausea and vomiting, stomach pain, feeling very thirsty or dry mouth (dehydration), passing urine more often than usual or passing greater amounts of urine than usual, blurred vision, unusually increased appetite, weight loss, fruity-smelling breath, flushed face and dry skin, feeling unusually sleepy or tired, and feeling lightheaded | | | ✓ |
| **Stomatitis** (mouth sores, redness and swelling of the lining of the mouth): painful, red, shiny or swollen gums, tongue, mouth or throat sores, blood in the mouth, difficult or painful swallowing or talking, dry mouth, mild burning, or pain when eating food, redness and swelling of the lining of the mouth | | ✓ | |
| **Urinary tract infection** (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine | | ✓ | |
| **COMMON** | | | |
| **Diarrhea, nausea, vomiting (severe):** dehydration, thirst, dark urine, decreased urine output, blood in urine, and weight gain (from retaining fluid) | | ✓ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

- Store at room temperature, 15°C to 30°C.
- Keep out of the sight and reach of children.
  Do not take this medicine after the expiry date (EXP) that is stated on the packaging. It refers to the last day of that month. Do not take this medicine if you notice any damage to the packaging or if there are any signs of tampering.
- Do not throw away any medicines via wastewater or household waste. Ask your healthcare professional how to throw away medicines you no longer use. These measures will help protect the environment.

**If you want more information about ITOVEBI:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website [www.rochecanada.com], or by calling 1-888-762-4388].

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